CLAIMS

We claim:

1. A method for identifying an agent that modulates activity of a membrane-spanning, signal-transducing (MSST) protein, the method comprising:

contacting a membrane-spanning, signal-transducing (MSST) protein with a candidate agent, the MSST protein having a conformationally-sensitive detectable probe positioned on or within a conformationally sensitive region of the MSST protein, wherein interaction of the MSST protein with an agonist or antagonist causes a conformational change in the conformationally sensitive region and a change in a detectable signal of the conformationally sensitive detectable probe; and

detecting the detectable signal of the conformationally sensitive detectable probe resulting from said contacting;

wherein detection of a change in a level of the detectable signal in the presence of the candidate agent relative to a control level of detectable signal indicates the candidate agent modulates activity of the MSST protein.

2. The method of claim 1, wherein the conformationally-sensitive detectable probe is a detectable chemical label attached to an amino acid residue of the conformationally sensitive region.

3. The method of claim 1, wherein the conformationally-sensitive detectable probe is a protease cleavage site and the detectable signal is a protease cleavage product.

4. The method of claim 1, wherein the conformationally-sensitive detectable probe comprises two protease cleavage sites, which cleavage sites flank a detectable polypeptide so that cleavage of the cleavage sites results in release of the detectable polypeptide, and wherein the detectable signal is the detectable polypeptide.

5. The method of claim 1, wherein the conformationally-sensitive detectable probe is an immunodetectable epitope and the detectable signal is present on a primary antibody that

specifically binds the epitope or on a secondary antibody that specifically binds the primary antibody.

6. The method of claim 1, wherein the conformationally sensitive region is in an intracellular loop, an extracellular loop, an N-terminal domain, or a C-terminal domain of the MSST protein.

7. The method of any one of claims 1-6, wherein the MSST protein is selected from the group consisting of a G protein coupled receptor (GPCR), an ion channel, or a transporter protein.

8. The method of claim 1, wherein the MSST protein is a G-protein coupled receptor (GPCR), and the conformationally sensitive region is an intracellular loop, an extracellular loop, an N-terminal domain, or a C-terminal domain of the GPCR.

9. The method of claim 8, wherein the conformationally sensitive region is a third intracellular loop of the GPCR, and the conformationally sensitive detectable probe is a detectable chemical label attached to one or more amino acid residues within the third intracellular loop so that a conformational change in the GPCR due to interaction with an agonist or antagonist causes a change in the detectable signal of the detectable probe.

10. The method of claim 9, wherein the detectable chemical label is attached to an amino acid residue corresponding to amino acid residue at position 265 in a β2-adrenergic receptor.

11. The method of claim 8, wherein the conformationally sensitive detectable probe is a protease cleavage site and the detectable signal is a protease cleavage product.

12. The method of claim 11, wherein the protease cleavage product is an N-terminal fragment of the GPCR, a C-terminal fragment of the GPCR.

13. An apparatus for detecting a molecule that modulates activity of a membrane-spanning, signal-transducing protein, the apparatus comprising:

a membrane-spanning, signal-transducing protein (MSST) of any one of claims 1-12; and

a immobilization phase to which the MSST protein is attached.

14. A kit for use in screening a candidate agent, the kit comprising:

a membrane-spanning, signal-transducing protein (MSST) of any one of claims 1-12.

15. The kit of claim 14, wherein the MSST protein is attached to an immobilization phase.